

Commentary: does immune suppression increase risk of developing acute myeloid leukemia?

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CONFERENCIA

HEMATOLOGÍA

Volumen 21 n° Extraordinario: 72-75

1^{er} Congreso Argentino de Trasplante de células progenitoras hematopoyéticas

2^{do} Congreso del LABMT

Keywords: AML,
Immune suppression,
Transplantation.

Abstract

Risk of developing some cancers is markedly increased in settings of immune suppression including after solid organ transplants and in persons with inherited immune-deficiency disorders and those with HIV-1 infection. These cancers include lymphomas, melanoma and non-melanoma skin cancers, kidney and cervical cancers, Kaposi sarcoma and neuroblastoma. There are no reports of an increased acute myeloid leukemia (AML) in settings of immune suppression. This is curious because some data suggest the immune suppression may be important in increasing AML risk in experimental settings, and that immune stimulation may be useful in treating AML. To see whether immune suppression is correlated with an increased risk of developing AML, we analyzed data from 248224 recipients of kidney (N = 217219) and

heart (N = 31005) transplants. Among the kidney transplant recipients, the standardized incidence ratio (SIR) for developing AML was 1.90 (95% confidence interval, 1.4–2.4; P<0.001). Among the heart transplant recipients, the SIR was 5.1 (3.4–7.1; P<0.001). These data suggest immune suppression increases risk of developing AML and that this risk is even higher following intense prolonged immune suppression. Implications for AML development and therapy are discussed.

Leukemia advance online publication, 26 August 2011; doi:10.1038/leu.2011.224

Substantial data suggest the immune system is important in AML development and therapy (reviewed in Smits et al.⁽¹⁾). On the other hand, risk of developing AML is not convincingly increased

in settings of immune suppression, like after solid organ transplants, in children with inherited immune deficiency disorders or in persons with HIV-1 infection. Also, spontaneous remissions are rare in AML (except for acute megakaryocytic leukemia in infants with Down syndrome). This contrasts with other cancers increased in these settings of immune suppression like lymphomas, melanoma and non-melanoma skin cancers, kidney and cervical cancers and Kaposi sarcoma (reviewed in Vajdic and van Leeuwen⁽²⁾). Why are some, but not all, cancer risks increased in settings of immune suppression? Some lymphomas are caused by or associated with uncontrolled proliferation of Epstein–Barr virus-infected B-cells (reviewed in Heslop⁽³⁾). However, in other lymphomas and other cancers, the mechanism for increased-cancer risk is unknown. The usual explanation is that these excess cancers arise because of ineffective immune surveillance. However, cancers developing after solid organ transplants and in inherited immune deficiency disorders are dissimilar to those occurring in age-adjusted controls like lung, colon and breast cancers. Something else must be happening.

There are three reports of an increased risk of leukemias after solid organ transplants supported by a meta-analysis^(4–7). However, these reports did not focus on AML. Leukemia risk, but not specifically AML, is also increased in persons with HIV-1 infection.

Diverse data support the notion that the immune system operates in AML. For example, immune abnormalities are reported in persons with AML. Also, some data suggest immune therapy can produce or lengthen remissions in persons with AML, including drugs like interferons, interleukins and lenalidomide. Interestingly, recipients of T-cell-depleted allogeneic hematopoietic cell transplants and recipients without graft-versus-host disease (GvHD) have higher AML relapse risks than those receiving T-cell-replete grafts and those with GvHD. Also, recipients of transplants from genetically-identical siblings have a higher AML relapse risk than recipients of transplants from HLA-identical siblings. These data suggest an immune-mediated, anti-AML effect (reviewed in Horowitz et al.⁽⁸⁾). Donor lymphocyte infusions also sometimes produce remissions in persons relapsing after an allotransplant which often correlates with

developing GvHD. Whether the aforementioned effects reflect an immune response to HLA- or non-HLA histocompatibility antigens (e.g. minor histocompatibility antigens) or a postulated, but unproved, immune response to leukemia-specific antigens (so-called graft-versus-leukemia effect; GvL) is unclear. Attempts to prove a leukemia-specific GvL-effect in humans with AML are, as yet, unconvincing. Also, results of most clinical trials of immune therapy of AML are disappointing. Although recent trials of immune therapy of AML are using dendritic cell vaccines, synthetic, AML-related peptides, natural killer cells and other approaches are reported, these are small, non-randomized studies and it is premature to comment on efficacy.

If the immune system is important in AML, why is AML not increased in settings of immune suppression? In a prior report of 185000 solid organ transplant recipients we observed an increased, combined risk of AML and myelodysplastic syndrome (MDS) amongst heart and/or lung and kidney allotransplant recipients. We suggested this might arise from mutagenic effects of azothiopurine which inhibits DNA mismatch repair mechanisms⁽⁹⁾. However, because that analysis combined AML and MDS, interpretation of the data was confounded. Consequently, we decided to focus on whether intense, prolonged immune suppression given after heart transplants might increase risk of developing AML (cases of MDS were excluded).

We used data from the Collaborative Transplant Study, which collects information on recipients of solid organ transplants since 1985, from 4300 transplant centers worldwide.

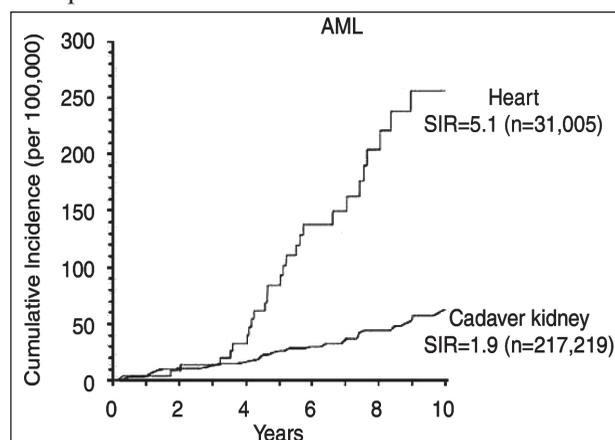


Figure. Cumulative incidence of AML amongst recipients of heart and kidney transplants.

Cancer incidence data were checked annually by questionnaire. Only AML in persons with a functioning transplant were included. Consequently, our data may underestimate AML incidence. Data were compared using Kaplan–Meier analyses. Data for expected AML incidence were obtained from a cohort of identical size, matched for age and sex from the Cancer Incidence in Five Continents, monitored for the same duration as the transplant cohort. The most appropriate regional reference registry was used for each transplant recipient. Data collection and processing were approved by the Data Protection Agency in Germany; all participating centers complied with local ethical and privacy regulations.

To see whether immune suppression correlates with an increased risk of developing AML, we analyzed data from 248224 recipients of kidney (N = 217219) and heart (N = 31005) transplants. Amongst kidney transplant recipients, the standardized incidence ratio for developing AML was 1.90 (95% confidence interval, 1.4–2.4; O/E = 54/29; P < 0.001). Amongst heart transplant recipients, the standardized incidence ratio was 5.10 (3.4–7.1; O/E = 31/6; P < 0.001; Figure). Interestingly, and in contrast to other posttransplant cancers, the increased risk of AML in heart transplant recipients did not begin until 3–4 years posttransplant, whereas the increased risk after kidney transplants began sooner and was linear.

Why the difference between heart and kidney transplant recipients? There are several possible explanations. Although both cohorts receive drugs that impair DNA-mismatch repair (like azothiopurine), immune suppression is more intense and prolonged after heart transplants. Also, diverse immune suppressive drugs are used more frequently and for a longer interval posttransplant after heart versus kidney transplants. Because detailed data on posttransplant immune suppression were unavailable, we were unable to adjust for potential confounding. Heart transplant recipients also have more diagnostic radiological studies and a few received total lymphoid radiation pretransplant. Consequently, heart transplant recipients are exposed to more ionizing radiations than kidney transplant recipients. Ionizing radiations are a known cause of AML. We were also unable to adjust for this possible confounding. However, we found

no significant difference in risk of developing MDS between heart and kidney transplant recipients (data not shown), as might be expected were exposure to radiation the critical factor. The sum of these considerations suggests AML risk is correlated with immune suppression, but only when it is intense and prolonged.

Intense immune suppression does not explain most cases of AML development. Some cases are caused by exposure to ionizing radiations, alkylating drugs (like busulfan, melphalan and nitrosoureas) and chemicals (like benzene). However, the cause(s) of most cases of AML is unknown. In other instances, including severe congenital neutropenia and Chediak–Higashi syndrome and Fanconi anemia, evolution to AML likely reflects the natural history of the disease and may be accelerated by exposure to molecularly cloned hematopoietic growth factors. This is unproved.

Our data indicate immune suppression is correlated with an increased risk of developing AML, especially when it is prolonged and intense. This conclusion may have implications for understanding the development of and therapy for AML.

Acknowledgements

Drs. John M Goldman, A John Barrett, Axel Hoos, Jeffrey Molldrem and Antoni Ribas kindly reviewed the typescript. We are grateful for support from the NIHR Biomedical Research Centre funding scheme.

Conflict of interest

RPG is an employee of Celgene Corp. GO declares no conflict of interest.

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